EXHIBIT 14

Epilepsia, **39**(8):887–892, 1998
Lippincott–Raven Publishers, Philadelphia

Pregnancies of Women with Epilepsy: A Population-Based Study in Iceland

*§Elias Olafsson, †Jon Thorgeir Hallgrimsson, §W. Allen Hauser, ‡Peter Ludvigsson, and *Gunnar Gudmundsson

*Department of *Neurology, †Obstetrics and Gynecology, and ‡Pediatrics, National University Hospital, Reykjavik, Iceland; and §Columbia University, Sergievsky Center, New York, New York, U.S.A.*

Summary: *Purpose:* Women with epilepsy who become pregnant are commonly considered to be at high risk for complications during pregnancy or delivery. The offspring are also considered to have increased risk of perinatal mortality, congenital malformations, and maturational delay. Because few of these studies are population based, potential bias exists because of selection.

Methods: We performed a historical population-based cohort study in Iceland to determine the prevalence of epilepsy among pregnant women, to identify pregnancy and delivery complications in women with epilepsy, and to determine the outcome of their pregnancies as compared with that in the general population of Iceland. We identified all women with active epilepsy who gave birth during a 19-year period in Iceland.

Results: In this population, 3.3 in 1,000 pregnancies involve mothers with active epilepsy. The frequency of adverse events (AE) during pregnancy in the women with epilepsy is similar to that observed among all live births in the population, but cesarean section was performed twice as frequently as in the general population. Perinatal mortality rate and mean birth weight are not significantly different in the offspring of women with epilepsy as compared with rest of the population. The risk of major congenital malformations (MGM) is increased 2.7-fold over that expected when a mother is treated with antiepileptic drugs (AEDs) during a pregnancy.

Conclusions: Our study indicates that the rate of complications of pregnancy in mothers with active epilepsy is low and similar to that of the general population with epilepsy. Use of AEDs by the mother during pregnancy significantly increases the risk of MGM in the offspring. **Key Words:** Epidemiology—Epilepsy—Pregnancy—Congenital malformations—Iceland.

Women with epilepsy who become pregnant are frequently considered to have a high risk of an adverse outcome (1,2). Numerous studies also indicate an increased risk of malformations (3,4) in offspring of mothers with epilepsy. Few population studies have determined the proportion of all pregnancies that occur in women with active epilepsy. We performed a population-based survey in Iceland to identify all women with epilepsy who gave birth during the 19-year period from 1972 through 1990. We wished to determine the proportion of pregnancies in women with active epilepsy among all pregnancies and to compare the proportion with complications of pregnancy, delivery, and outcome in those with and without epilepsy.

Accepted March 3, 1998.
Address correspondence and reprint requests to Dr. E. Olafsson at Department of Neurology, National University Hospital (Landspitalinn), 101 Reykjavik, Iceland.

PATIENTS AND METHODS

Index cases were all women with epilepsy treated with antiepileptic drugs (AEDs) during pregnancy or during a 5-year period preceding the pregnancy. All the women were residents of Iceland and gave birth in Iceland during the study period. Only live births, products of pregnancies progressing at least through week 28 of gestation were included. The study period was from January 1, 1972 to December 31, 1990.

Index cases were identified from records of all the hospitals in the country where children are born. Supplemental information was provided by records of the EEG laboratories in the country and records of private physicians. We believe we have identified all cases in the population meeting entry criteria.

Standardized obstetrical records were adopted in Iceland in 1972. These records contain information about the progression of pregnancy, associated medical conditions, medications used during pregnancy, and findings of the newborn physical examination. These obstetrical records were reviewed to identify women with the diag-

nosis of epilepsy. Etiology of epilepsy, medication status, seizure type and frequency, pregnancy complications, and the status of the newborn were determined from these records, supplemented by information obtained from review of hospital and physician records (primarily neurologists).

Population information regarding birth weight and frequency and type of congenital anomalies from 1982 through 1990 was provided by the Icelandic Birth Registry, which contains data on all births in the country recorded at the time of each mother's discharge. For comparison with information obtained from the birth registry, only MCM identified or suspected during the first week of life were included. In our analysis, children with postural deformities (foot deformities), hernias (inguinal and umbilical), and hydrocele are not included. For determination of standardized morbidity ratio (SMR) for all MCM, we included as affected 1 child with a cardiac murmur identified at birth but subsequently shown to be benign. For determination of type of specific SMR, only the verified cases were included. This allowed comparison with published population data on these anomalies in the Icelandic population. Demographic information was provided by the Statistical Bureau of Iceland

Statistical methods

Proportions were compared by chi-square test (5). The binomial distribution was used to compare the proportion of affected cases with that observed in the population. Student's t test was used to compare means, and the one-sample t test was used to compare an observed mean with the population value. SMR was used as a measure of difference between observed and expected frequency of adverse events (AE).

RESULTS

The average Icelandic population during the study period was 231,778. The number of live births in Iceland during the 19 years was 82,483 from 81,473 pregnancies. Most of the children were born in a hospital, and a large proportion (two-thirds) of all deliveries were in the National University Hospital (Landspitalinn) in Reykjavik. Less than 1% of children were born at home.

During this period, there were 266 pregnancies to 157 women with active epilepsy, yielding 268 liveborn children. The children included one set of triplets. There were also two stillbirths to index mothers; these are considered only for determination of perinatal mortality.

Epilepsy

Seizure type

The distribution of the cases (n = 157) by seizure type was as follows: absence, 1; absence and generalized tonic-clonic seizures (GTCS) 12, GTCS, 64; GTCS and myoclonus, 10; myoclonus only, 1; focal motor seizures, 4; focal motor seizures and GTCS 9; simple partial seizures other than focal motor (SPS), 1; SPS and complex partial seizures (CPS), 6; CPS, 14; SPS and GTCS, 5; CPS and GTCS, 23; and GTCS with Todd's paralysis, 1; seizure type was unknown in 6 women.

Age of mother at onset of seizures

Age of onset was as follows: 0–9 years, 36 (23%); 10–19 years, 88 (56%); 20–29 years, 28 (18%); 30–39 years, 3 (2%), and unknown, 2 (1%).

Etiology

The epilepsy was idiopathic/cryptogenic in 85% (134 of 157) and symptomatic in 13% (20 of 157). Information was insufficient to determine cause for 2% (3 of 157). The known causes were as follows: CNS infection, 6; cerebrovascular disease, 5; neurological deficit from birth, 3; head injury, 3; brain tumor, 2; and degenerative neurologic disease, 1.

EEG

Results of EEG were available for 98% (154 of 157) of the mothers. Most had undergone multiple EEGs. Forty-seven had normal EEGs, 54 had generalized epileptiform changes, 32 showed focal epileptiform changes, 3 had unspecified epileptiform changes, 7 showed generalized slow activity, and 11 showed focal slow activity. Results for 2 mothers, 1 of whom was foreign born, were not available for review. No EEG was obtained in 1 woman with SPS.

Epileptic syndromes

The following epileptic syndromes were identified: juvenile myoclonic epilepsy (11 mothers), GTCS on awakening (2 mothers), and pyknolepsy (3 mothers). No specific syndrome was identified in 133. The information was insufficient to allow classification in 8.

AEDs

AED status during pregnancy was known for 263 (99%) of 266 pregnancies. Among the 263 mothers, 221 (84%) were treated with AEDs. During 42 (16%) of the pregnancies, the mothers were not treated with AEDs. The distribution of number of AEDs is shown in Table 1, type of AED is shown in Table 2.

Seizure occurrence during pregnancy

Information on seizure occurrence was available for 155 of the 266 pregnancies. Seizures occurred during 93 (60%) of these 155 pregnancies, and 86% (80) of the mothers were treated with AEDs as compared with 75% (47) of the 62 mothers known not to have seizures (p = 0.16, NS).

Pregnancy and delivery

Prevalence

In all, 266 pregnancies of women with active epilepsy were identified during the study period, for a prevalence

TABLE 1. *MCM and number of AEDs*

No. of AEDs	MCM (n = 15)	All pregnancies (n = 263)[a]	Percentage with MCM	SMR (95% CI)
Population baseline[b]			2.2	
None	2	42	4.8	2.2 (0.3–0.8) NS
One	4	118	3.4	1.5 (0.4–3.9) NS
Two	7	78	9.0	4.1 (1.7–8.5)
Three or more	2	25	8.0	3.6 (0.4–13.1) NS
Total receiving AEDs	13	221	5.9	2.7 (1.4–4.5)

MCM, major congenital malformation; AEDs, antiepileptic drugs; SMR, standard morbidity ratio; CI, confidence interval.

[a] The drug status was unknown for 3 (1%), and these are not included.

[b] Icelandic Birth Registry: all births in Iceland 1982–1990.

of 3.3 pregnancies in women with active epilepsy for every 1,000 pregnancies in the population.

Pregnancy and delivery complications

The following information regarding pregnancy and delivery was derived from the maternal record. Breech presentation occurred in 12 (5%) deliveries. The numbers of AEDs received by the 12 mothers during the pregnancy were none (n = 1), one (n = 3), two (n = 2) and three (n = 2), which is not significantly different from the rest of the women (p = 0.6, 3 *df*, NS).

Cesarean section was performed in 35 (13%, 35 of 266 deliveries as compared with 8.8% [7,139 of 81,473] in the Icelandic population (p = 0.01). The indications in the 35 cesarean sections were as follows: previous cesarean section (n = 7), malpresentation (n = 4), breech presentation (n = 3), seizure during delivery (n = 3), status epilepticus during delivery (n = 1), "epilepsy" (n = 4), preeclampsia (n = 2), imminent asphyxia (n = 2), disproportion (n = 2), cervical dystocia (n = 1), prolapse of the umbilical cord (n = 1), prolonged delivery (n = 1), premature separation of placenta (n = 1), difficult previous delivery (n = 1), low implantation of placenta (n = 1), and maternal heart disease (n = 1). Forceps were used in 8 (3%) of deliveries because of prolonged delivery (n = 6) or imminent asphyxia (n = 1) and for unspecified reasons (n = 1). Prolonged labor defined as labor (lasting >24 h) occurred in 12 deliveries. The mothers were treated with no AED (n = 1) one AED (n = 5), two AEDs (n = 5), and three AEDs (n = 1). There was no difference in number or type of AEDs as compared with the rest of the mothers (p = 0.7, NS). During delivery, four women had GTCS; included in these episodes was the only recorded episode of convulsive status epilepticus during any of the pregnancies. Other complications included postpartum bleeding in the 1 woman who received no AEDs during pregnancy. One woman had placental retention. Imminent asphyxia in the fetus was noted in three instances.

The child

Perinatal mortality is defined as stillborn (after week 28 of gestation) or death during the first week of life. Two study mothers gave birth to a stillborn child and 1 child with anencephalus died during the first week of life. This perinatal mortality of 11.2 in 1,000 is not significantly different from that in the general population: 8.7 in 1,000 (367 of 42,197) for the period 1976–1985 (6); odds ratio (OR) 1.5 [95% confidence interval (CI) 0.3–4.1].

Prematurity is defined as gestational age <37 weeks at delivery. Sixteen pregnancies resulted in premature birth

TABLE 2. *MCM and type of AED exposure during pregnancy*

Type of AED[a]	MCM (n = 15)	All children (n = 265)[b]	Percentage affected	SMR (95% CI)
None	2	42	4.8	2.2 (0.3–8.0) NS
PB	8	92	8.7	4.0 (1.7–7.9)
PHT	7	91	7.7	3.5 (1.4–7.2)
VPA	2	44	4.5	2.0 (0.2–7.2) NS
PRM	2	31	6.5	2.9 (0.3–10.3) NS
SUL	2	5	40.0	20.03 (2.4–72.2)
CBZ	1	84	1.2	0.5 (0.1–3.1) NS
DZP	1	2	50.0	25.0 (0.6–139.2) NS

PB, phenobarbital; PHT, phenytoin; VPA, valproate; PRM, primidone; SUL, sulthiame; CBZ, carbamazepine; DZP, diazepam; other abbreviations as in Table 1.

[a] The patients were also receiving clonazepam (3) and nitrazepam (1), but did not have offspring with MCM.

[b] Three children (1%) for whom drug exposure was not known are not included.

of 18 children (7%), including a set of triplets born after 32 weeks gestation. The other 16 were born between 32 and 37 weeks gestation. The number of AED prescribed for the mothers was as follows: none (n = 1), one (n = 10), two (n = 3), and three (n = 2). The number and distributions of AEDs among mothers during pregnancy was not significantly different from that of the rest of the mothers with epilepsy (p = 0.3 NS, 3 *df*).

Mean birth weight for the 250 children born at term was 3,601 g, slightly lower than the population mean of 3,647 g. The different was not statistically significant (one-sample *t* test, p = 0.2, NS). The medication status was known for 247 of the 250 women. The mean birthweight of the 206 children of mothers treated with any AEDs was 3,591 g. The mean birthweight of the 41 children born to mothers not treated with AEDs was 3,640 g. The birthweight by number of AEDs was as follows: one (n = 108), 3,630 g; two (n = 75), 3,574 g; and three or more (n = 23), 3,467 g. The trend for birthweight decrease with increasing number of AEDs was not significant (p = 0.5).

MCM suspected at birth were evident in 5.7% of the offspring of mothers with epilepsy as compared with 2.2% in the general population (SMR 2.6, 95% CI 1.5–4.3). This includes the 1 child with the cardiac murmur subsequently considered benign. We excluded from this and from subsequent analysis 1 child who was noted in the first year of life to have reduplication of the ureter. In addition, the following conditions identified at birth were not included as MCM: Down syndrome (n = 1), hydrocele (n = 1), clubfoot deformity (n = 1), and small umbilical hernia (n = 1).

Specific MCM

Specific MCM are shown in Table 3. Six cases of cleft lip/palate were noted; 0.5 could have been expected, [SMR 12, 95% CI 4.4–26.2 (6 in 268 and 154 in 82,483) (7)]. Three cases of hypospadias were noted; 0.3 could have been expected (SMR 10, 95% CI 2.1–29.2). Four children were suspected at birth to have congenital heart disease (CHD). Based on population data for suspected heart disease at birth (0.5%, 194 in 38,595), 1.3 would have been expected (SMR 3.1, 95% CI 0.8–3.9, NS). Three of the 4 children with CHD suspected at birth later had CHD verified. Two had small ventricular septal defects which were considered "mild." One had persistent ductus arteriosus requiring surgery, and the condition was considered "severe." Based on the incidence of severe CHD in Iceland (8) of 0.2% (45 in 20,917), we would have expected 0.5 cases (SMR 2, 95% CI 0.05–11.1, NS). One case of spina bifida was noted; 0.1 could have been expected.

TABLE 3. *MCM (n = 15)*

Type of MCM	n	No. of AEDs	Type of AED
Anencephalus	1	2	PHT, PB
Cleft lip/palate	6	3,3,1,2,2,2	VPA(2), PRM(2), PB(5), PHT(2), SUL(1), DZP(1)[a]
Congenital heart disease	3	1,1,2	PB(2), CBZ(1), PHT(1)
Hypospadias	3	0,0,1	PHT
Microcephaly	1	2	PHT, PB
Spina bifida	1	2	PHT, SUL

Abbreviations as in Table 1.
[a] DZP used as AED.
[b] One child had patent ductus arteriosus and 2 had small ventricular septal defects.

Etiology of epilepsy and MCM

Thirteen mothers of children with MCM had idiopathic epilepsy. Two others had symptomatic epilepsy; 1 was mentally retarded, and the other developed epilepsy subsequent to embolic stroke association with CHD. The distribution by etiology is identical among mothers of children with congenital malformations as compared with the rest of the mothers (p = 1.0).

Generalized spike wave (GSW) on EEG and MCM

One mother of a child with MCM (7%) had GSW on EEG as compared with 34% (53 of 157) (p = 0.06).

AEDs and MCM

There was no significant increase in number of malformations in offspring of mothers treated with AEDs (5.9%) as compared with those not treated with AEDs (4.8%). There was a trend for increasing number of MCM with increasing number of AEDs. A significant increase in number of MCM was evident in mothers receiving two AEDs (Table 1). The proportion of offspring of mothers treated with a specific drug is shown in Table 2. Three AEDs (phenobarbital, phenytoin, sulthiame) were associated with a significant increase in risk for MCM.

Time trends in AEDs treatment and MCM

During the first half of the study period, 108 mothers were receiving AEDs: 49 received one, 40 received two, and 19 received three or more. Eight MCM were noted among their children. During the latter part of the study period, 113 mothers were receiving AEDs: 69 received one, 38 received two, and 6 received three or more (6). Seven of their children had MCM. During the latter period of the study, significantly more mothers were receiving monotherapy. During the first part of the study significantly more mothers were receiving three AEDs (p = 0.002, chi-square for trend).

Seizure during pregnancy and MCM

Information regarding occurrence of seizures was available for 59% of the pregnancies (Table 4). Known maternal seizures during pregnancy were associated with

TABLE 4. *MCM and seizures during pregnancy*

Seizures during pregnancy	MCM (n = 15)	All children (n = 268)	Percentage of children with MCM	SMR (95% CI)
Yes	8	95	8.6	3.8 (1.6–7.5)
None	1	62	1.6	0.7 (0.02–4.0) NS
Not known	6	111	5.4	2.5 (0.9–5.5) NS

Abbreviations as in Table 1.

a significant increase in MCM (SMR 3.8) as compared with the number expected. There was no increase in MCM in offspring of mothers who did not have seizures during the pregnancy.

DISCUSSION

We believe we have identified all women with active epilepsy who gave birth to a living child in Iceland during the 19-year study period: 3.3 of every 1,000 pregnancies in the general population occurred in women with active epilepsy. This finding is similar to the numbers predicted by other investigators (9,10).

The frequency of cesarean section among the study group was almost twice that in the general Icelandic population. In a Finnish study (11), no increase in the rate of cesarean section among mothers with epilepsy was reported. One fourth of the cesarean sections in the present study were directly attributable to the epilepsy itself. Prolonged labor was not associated with the number of AEDs with which the mother was treated during the pregnancy. Breech presentation occurred in 5% of deliveries. The number and distribution of AEDs prescribed for the mothers with breech presentation was similar to that of the other mothers with epilepsy. In a study in England (12), Robertson reported an increase in breech presentations among mothers with epilepsy (12%) as compared with that among >12,000 deliveries (4%) at a general hospital. In Norway (1), Eganaes noted no difference in the rate of breech presentations among deliveries of mothers with epilepsy (3.3%) as compared with controls (3.1%).

In the present study, the increase in perinatal mortality was not stastically significant (SMR 1.5). Data on this topic in the literature are conflicting (1,4,11,13).

Premature birth occurred in 7% of the pregnancies. The type and frequency of AEDs prescribed was not different among mothers of premature children as compared with the rest of the cases.

Birthweight in term infants of mothers with epilepsy was not different from that of the general population. This finding is similar to that of Waters et al. (13).

The rate of MCM in children of mothers treated with AEDs was increased 2.7-fold as compared with that in the Icelandic population (5.9 vs. 2.2%). The rate of MCM was increased in offspring of mothers with epilepsy not treated with AEDs, but this finding did not reach statistical significance.

To compare our findings properly with population data, we limited MCM to those diagnosed or suspected in the first few days of life. This approach may underestimate the true proportion of offspring with MCM. Several conditions can be reliably identified at birth, but frequently MCM involving the cardiovascular and genitourinary systems are not identified at birth (14). The risk of cleft lip/palate in offspring of mothers with epilepsy is 12-fold that expected in the general population. The point estimate is higher than that reported in other population-based studies conducted in that time period, but a consistent reported increase was noted during the study period (14–18). The decreased risk of cleft lip/palate reported in the most recent population-based study (15) was attributed to changes in AED treatment.

The risk of hypospadias was increased 10-fold. The point estimates both for suspected CHD at birth and for severe CHD were increased, but did not reach statistical significance. The mother of the 1 child with spina bifida was treated with phenytoin and sulthiame. The expected frequency of spina bifida in the Icelandic population during this time period was 1 in 2,600 live births. We cannot interpret the meaning of a single case in this series.

Significantly fewer AEDs were used by pregnant mothers during the last half of the study than during the first half, but the rate of MCM was the same for both periods. In a study in Montreal (19) Oguni et al. reported a decrease over time in both the rate of MCM in offspring and number of AEDs received by the mothers. The decrease in birth defects in the Montreal study was attributed to a reduction of "postural deformities or hernias." Because the rate of "developmental defects" (including cleft lip, CHD, and neural tube defects) was unchanged, the results of Oguni et al. (15) are similar to ours in the present study.

The mothers of the infants with MCM were not more likely to have GSW epileptiform changes as compared with the rest of the group ($p = 0.06$). It has been suggested that spina bifida occulta is more common among patients with juvenile myoclonic epilepsy, but a recent study by Sundquist et al. (20) did not confirm this.

In the present study, known seizures during pregnancy were associated with a significant increase in risk for MCM (Table 4). In a study in Rochester, Annegers et al. (14) did not find MCM to be associated with maternal seizures during pregnancy. AED treatment during pregnancy may be a confounder for this association, although the proportion of mothers receiving any medication among those with and without known seizures during pregnancy was not significantly different in the present study.

Our data indicate that the complications of pregnancy are infrequent and the pregnancies of mothers with active

epilepsy treated with AEDs can be expected to progress uneventfully even if careful monitoring is needed. These data do not warrant categoric designation of such pregnancies as "high risk."

The risk of MCM in the offspring when the mother is treated with AEDs is increased almost threefold. The highest rate of MCM was assocaited with sulthiame, a drug no longer available. Of AEDs currently used, both PB and PHT are associated with an increased risk of MCM. Carbamazepine (CBZ) appears to be associated with the lowest risk of MCM, and no MCM were associated with CBZ monotherapy. The risk of MCM in the offspring of women with epilepsy who were not treated with AEDs was doubled, but this finding was not statistically significant. There was a trend toward increased number of MCM with increasing number of AEDs received during pregnancy (Table 1), but the trend did not reach statistical significance. Because both MCM and fetal exposure to AEDs were infrequent in the population, prospective studies of the association of specific MCM with specific AEDs would have to be very large.

REFERENCES

1. Egenaes J. Outcome of pregnancy in women with epilepsy—Norway, 1967–1978: complications during pregnancy and delivery. In: Janz D, et al., eds. *epilepsy, pregnancy and the child.* New York: Raven Press, 1982.
2. Wilhelm J, Morris D, Hotham N. Epilepsy and pregnancy—a review of 98 pregnancies. *Aust NZ J Obstet Gynaecol* 1990;30:290–5.
3. Dravet C, Julian C, Legras C, et al. Epilepsy, antiepileptic drugs, and malformations in children of women with epilepsy: a French prospective cohort study. *Neurology* 1992;42(suppl 5):75–82.
4. Sonneweld SW, Correy JF. Outcome of pregnancies complicated by epilepsy in Tasmania 1981–1988. *Aust NZ J Obstet Gynaecol* 1990;30:286–9.
5. Altman DG. *Practical statistics for medical research.* London: Chapman & Hall, 1991.
6. Georgsdottir I, Geirsson RT, Johannsson JH, Biering G, Snaedal G. Classification of perinatal and late neonatal deaths in Iceland. A survey from a defined population. *Acta Obstet Gynecol Scand* 1989;68:101–8.
7. Björnsson A, Johannesdottir G. Rannsóknir á skarðasjúklingum: yfirlitsgrein. [Overview and follow-up study of patients with cleft palate]. *Læknablaðið [Iceland Med J]* 1996;82:703–12.
8. Sigfusson G, Helgason H. Nýgengi og greining meðfæddra hjartagalla á Íslandi. [Incidence and diagnosis of congenital heart disease in Iceland]. *Læknablaðið [Iceland Med J]* 1992;79:107–14.
9. Gaily E. Development and growth of children of epileptic mothers: a prospective controlled study. Thesis. University of Helsinki, Helsinki, Finland, 1990.
10. Lindhout D, Omtzigt JGC. Pregnancy and risk of teratogenicity. *Epilepsia* 1992;33(suppl 4):S41–8.
11. Hiilesmaa VK, Bardy A, Teramo K. Obstetric outcome in women with epilepsy. *Am J Obstet Gynecol* 1985;152:499–504.
12. Robertson IG. Breech presentation associated with anticonvulsant drugs. *J Obstet Gynaecol* 1984;4:174–7.
13. Waters CH, Belat Y, Gott PS, Shen P, De Giorgio CM. Outcome of pregnancy associated with antiepileptic drugs. *Arch Neurol* 1994;51:250–3.
14. Annegers JF, Hauser WA, Elveback LR, et al. Congenital malformations and seizure disorders in the offspring of parents with epilepsy. *Int J Epidemiol* 1978;7:241–7.
15. King PB, Lie RT, Irgnes LM. Spina bifida and cleft lip among newborns of Norwegian women with epilepsy changes related to the use of anticonvulsants. *Am J Public Health* 1996;86:1454–6.
16. Bjerkedal T, Bahna SL. The course and outcome of pregnancy in women with epilepsy. *Acta Obstet Gynecol Scand* 1973;52:245–8.
17. Speidel BD, Meadow SR. Maternal epilepsy and abnormalities of the fetus and newborn. *Lancet* 1972;2:839–43.
18. Hill L, Murphy M, McDowall M, Paul AH. Maternal drug histories and congenital malformations: limb reduction defects and oral clefts. *J Epidemiol Commun Health* 1988;42:1–7.
19. Oguni M, Dansky L, Andermann E, Sherwin A, Andermann F. Improved pregnancy outcome in epileptic women in the last decade: relationship to maternal anticonvulsant therapy. *Brain Dev* 1992;14:371–80.
20. Sundquist A, Gustafsson J, Tomson T. Vertebral arch nonfusion and juvenile myoclonic epilepsy. *Epilepsia* 1994;35:328–31.